Advanced Therapeutics: Managing the Severe and Refractory Eczema Patient

Jennifer S. Kim, MD
Assistant Professor of Pediatrics
Jaffe Food Allergy Institute
Mount Sinai School of Medicine, New York, NY

Peter A. Lio, MD
Assistant Professor of Clinical Dermatology & Pediatrics
Director, Eczema Care and Education Center
Northwestern University Feinberg School of Medicine, Chicago, IL

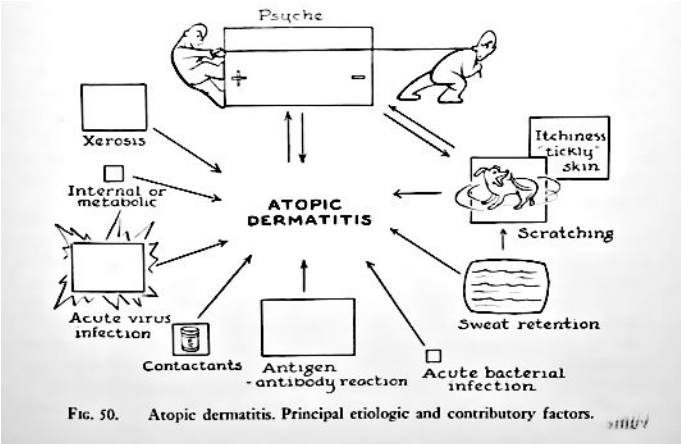
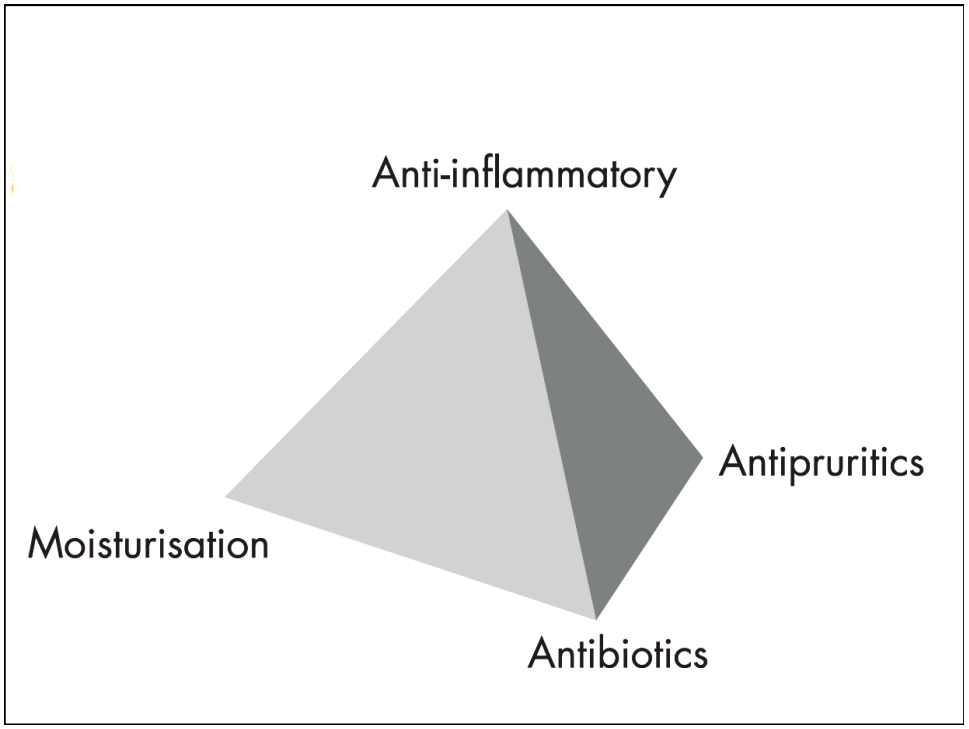


FIG. 50. Atopic dermatitis. Principal etiologic and contributory factors.

Pillsbury DM, Kligman AM, Shelley WB. *A manual of cutaneous medicine, by Donald M. Pillsbury, Walter B. Shelley [and] Albert M. Kligman. Philidelphia. Saunders, 1961.*



Diagnostic Considerations

QUESTION: Foods and AD

- How do you assess the contribution of food allergy (FA) in severe eczema?

FA and AD

- FA and AD are highly associated.
  - Up to 37% of children <5 years with moderate to severe AD will have IgE-mediated FA
- Whether FA can exacerbate AD is controversial (lack of well-designed avoidance trials in patients with AD)
  - Several studies found improvement in pruritus when patients with egg allergy and AD were placed on egg-free diet

Lever R et al, Pediatr Allergy Immunol 1998

FA and AD misconceptions

- Eczematous flares can be erroneously attributed to foods by patient/parent
  - May be precipitated by irritants, humidity, change in temperature, infections
- Thus, AD may continue to flare in patients with FA despite strict elimination diet

Practical considerations: when to consider testing to foods in AD

- When proper skin care is not working in child
- When eczema flares are consistently associated with a specific food as a trigger
- If the child is not growing well

*Milk, egg, and peanut are the most common allergens in young children *(test judiciously)*

The younger the child and the more severe the AD, the greater likelihood that child has FA

Guillet G & MH, Arch Dermatol 1992

QUESTION: Foods and AD

- If you eliminate a food (e.g. eggs or milk) for a period of time to see if it is contributory, are you increasing the risk of *anaphylaxis* when you reinstitute that same food?

QUESTION: Foods and AD

Actually 2 questions:

- If you eliminate a food (e.g. eggs or milk) for a period of time to see if it is contributory, what is the risk of *a reaction* when you reinstitute that same food?

- What are the risks for a severe reaction or *anaphylaxis*?

Factors to consider before reintroducing foods

- Has food elimination helped AD?
- How long has food been eliminated?
- How long/frequently was food in diet prior to elimination? (Is this an infant or teenager?)
- Has testing been performed? If so, results?

*When tolerance develops to food, reintroduction of food will NOT cause AD to recur or worsen.

Sampson & Scanlon, J Peds 1989

- 75 children (3-18 mos) with AD diagnosed with FA using DBPCFC
- Milk, peanut, egg most common
- Allergen-restricted diet for 1-2 years → repeat DBPCFC: 31% FA resolved
- Patients with both skin + resp sx at initial OFC were *less* likely to have resolved FA
  - compared to those with skin only or skin + GI sx

Risk factors for severe food reactions

- Asthma!
- Amount of allergen ingested
- Form of food (raw, cooked, processed)
- Age of patient (teen, young adult)
- Degree of sensitization (threshold dose) at time of ingestion
- Rate of absorption (empty stomach, exercise, alcohol intake, etc)

QUESTION: Foods and AD

- What is the status of food patch testing in severe AD? Is there any role for it in refractory cases, wherein food-specific IgE-guided diet manipulation has already been attempted but with limited success?

Atopy Patch Test (APT)

- 2010 Food Allergy Guideline 8: NIAID-sponsored EP suggests that APT should not be used in routine evaluation of non-contact FA
  - No standard reagents available
  - No studies that specifically address APT methodology met inclusion criteria for report
  - Two large studies conclude there is no significant clinical value in using APTs for FA diagnosis

Mehl et al, JACI 2006 & Keskin et al, Ann Allergy Asthma Immunol 2005

QUESTION: Foods and AD

- Effect of super high IgEs on specific positive predictive value for milk, eggs, etc.?
- How to interpret without challenge?

"Super high" IgE levels

- Elevated total IgE levels frequently found in atopic individuals
- No studies to date provide support of use of total IgE in interpreting specific IgE levels
- Predictive value of ratio of sIgE to total IgE compared with DBPCFC for diagnosis of FA. Conclusion: Ratio offers **no** advantage over sIgE alone.

Mehl A et al, Allergy 2005

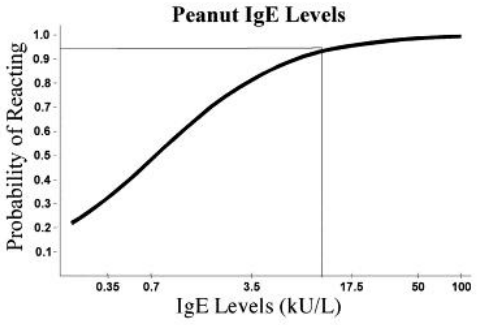
Predictive value of food allergen-specific IgE levels

95% Predictive Level

Allergen	[kU$_A$/L]	PPV
Egg	7	98
- Infants ≤ 2 yrs[+]	2	95
Milk	15	95
- Infants ≤ 2 yrs[++]	5	95
Peanut	14	100
Fish	20	100
Tree nuts[+++]	~15	~95
Soybean	30	73
Wheat	26	74

\+ Boyano MT, et al. Clin Exp Allergy 2001; 31(9):1464-9.
++ Garcia-Ara C, et al. J Allergy Clin Immunol 2001; 107(1):185-90.
+++ Clark AT, Ewan P. Clin Exp Allergy. 2003; 33(8):1041-5

PPV = Positive predictive value



Increasing probability of clinical reactivity with increasing level of food-antigen specific IgE value; note: values <0.35 do not exclude allergic reactivity

Journal of Allergy and Clinical Immunology 2004; 113:805-819

QUESTION: Infections

- Is there any role for skin culture, as opposed to empiric use if anti-staphylococcal systemic antibiotics in severe AD flares?
- Occasional furuncle or recurrent clinical staph infections w/o infections, IgE > 10,000. No family history of Hyper IgE syndrome?

Infections

- Staph is incredibly common (> 90% in severe cases)
- Usually I do not culture anymore
- For some reason, MSSA > MRSA in this group so far…
- But in refractory cases, or if pustules or ulcers, culture could be important, esp immunosuppressed patients… so common, however

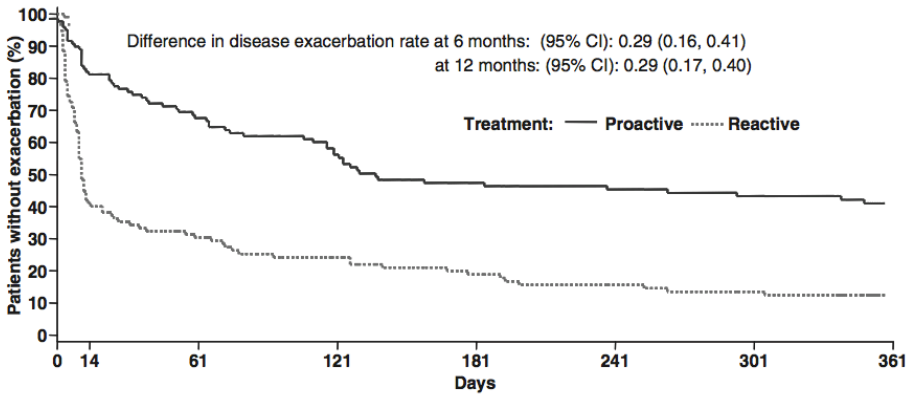
Therapeutics

QUESTION: TCIs

- How often is combination therapy with both a moderate potency corticosteroid and a topical immuno-modulator more helpful than either one alone?
- What is the most appropriate role for the use of calcineurin inhibitors?

- Maintenance tacrolimus twice weekly when eczema clear
- Was effective in reducing the number and frequency of disease exacerbations and improving health-related QoL

Wollenberg A, et al. Economic evaluation of maintenance treatment with tacrolimus 0.1% ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol. 2008 Dec;159(6): 1322-30



Wollenberg A, Reitamo S, Girolomoni G, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. European Tacrolimus Ointment Study Group. Allergy. 2008 Jul;63(7):742-50.

Synergy

- I have used a topical steroid in the AM and then a TCI in the PM; for some cases of severe, refractory disease, I think there may be synergy
- Also a nice way to transition for patients who feel stinging and burning with TCIs
- "The results of our small retrospective study suggest that TCPO may be more effective than either 0.1% tacrolimus or clobetasol propionate 0.05% ointment monotherapy in the treatment of recalcitrant CLE."

Madan V, August PJ, Chalmers RJ. Efficacy of topical tacrolimus 0.3% in clobetasol propionate 0.05% ointment in therapy-resistant cutaneous lupus erythematosus: a cohort study. Clin Exp Dermatol. 2010 Jan;35(1):27-30.

QUESTION: Phototherapy

- Some area dermatologists are still using UV radiation in the treatment of eczema, even in young children. What is the role of UV treatment?

Phototherapy

- 1903 Nobel Prize in Medicine: Niels Ryberg Finsen, Danish pioneer of phototherapy
- *Om Lysets Indvirkninger paa Huden* (On the effects of light on the skin)
- Probably multiple mechanisms including increasing vitamin D which in turn enhances cathelicidin

Phototherapy

- Works in about 60% of refractory cases
- NB-UVB (311nm) seems very safe

Problems:
-Time
-Money (co-pays, parking, etc)

Home units…

QUESTION: Topical Steroids

- What is the highest class of steroids for how long with what frequency is your top dose for kids?

Topical Steroids

- No easy answer here… to some extent, I will use whatever it takes, even class 1 steroids on the face for brief bursts
- Pearl: for patients saying "as soon as I stop, it come RIGHT BACK" or "I have to use EVERY DAY", steroid potency is probably too low*

*Provided all other areas of the tetrad are being maximized, of course

QUESTION: Systemic Medications

- How long is your trial of cyclosporine?

Cyclosporine: From PeDRA

- Rapid
- 5mg/kg/d, 300mg/d max
- Monitoring: BP q wk x 4 then q mo CBC, LFTs, BUN, Cr, CMP, uric acid, lipids monthly x 3 then every 8 wks
- Maintain x 3 mo then taper
- Limit to 1 yr
- (Pediatric Dermatology Research Alliance)

Imuran: From PeDRA

- Onset is 4-6 weeks
- Can use concurrent pred x 1 mo
- Baseline TPMT if normal: 2.5-3.5 mg/kg/d
- If intermediate TPMT: 1mg/kg
- Monitoring: CBC, LFTs, BUN, Cr at 2,4,8,12 wks then every 8 wks
- Maintain x 3 mo then taper
- Limit to 2 yrs

QUESTON: Antibiotics

- When and how long to treat with antibiotics for chronic management?
- In recalcitrant patient, if staph superantigen can play a role, and skin has staph w/o clinical infection, any role to try and decrease staph load?

Antibiotics

- Since the Paller bleach bath study, I have used less topical and systemic antibiotics than ever
- Bleach baths: qd when flaring, biweekly as maintenance
- Staph is ubiquitous and, for some reason, MRSA seems to be a less common colonizer here; I usually do not culture anymore
- Cephalexin still seems to be most helpful
- Usually 14 days, though I have used TMP-SMX longer term in some severe cases

QUESTION: Yeast

- Recalcitrant patient and malassezia/ pityrosporum - if no clinical infection, leave it alone? KOH prep? What if positive?

Yeast

- A few interesting papers on head and neck dermatitis in young adults showing that Malassezia allergy may play a role
- Consider: Itraconazole daily x 2 mo then long-term weekly treatment 100mg po qd
- This has not worked well for me… but I do try and I have had 2 patients respond well… and about 10 fail the treatment

Darabi K, et al. The role of Malassezia in atopic dermatitis affecting the head and neck of adults. J Am Acad Dermatol. 2009 Jan;60(1):125-36.

QUESTION: Pruritus

- What role if any for anti-anxiety meds, sleep aids in children with intractable scratching and sleeplessness?

Pruritus

- Data is poor that anti-pruritics help our more severe cases (I wish they did help!)
- Even in my severe cases, I usually am able to taper these off once skin is better
- Hydroxyzine in kids; doxepin or mirtazapine in older patients can really help get through the night due to sedative effects

QUESTION: Immunotherapy

- Immunotherapy to house dust mites (HDM)?
- How effective IT might be in bad AD?

Allergen Immunotherapy: 3rd update of practice parameter (2011)

- Summary Statement 8: There are some data indicating that immunotherapy can be effective for atopic dermatitis when associated with aeroallergen sensitivity
- Bussman et al, JACI 2007: In review of 4 placebo-controlled studies, statistical analysis showed significant improvement in symptoms in AD patients who received SCIT.

Subcutaneous immunotherapy (SCIT)

- Werfel T et al, Allergy 2006
  - Multi-center, randomized, double-blind study of 51 adults with AD
  - Maintenance doses of 20, 2000, and 20,000 SQ-U weekly for 1 year
  - HDM SCIT effectively reduced AD in dose-dependent manner, as measured by SCORAD and topical corticosteroid use

Subcutaneous immunotherapy (SCIT)

- Bussman et al, Clin Exp Allergy 2007
  - Open pilot study to evaluate the benefit of HDM SCIT x 6 mos in 25 AD patients with HDM sIgE
  - Subjective and objective SCORAD improved significantly within 4 weeks of treatment
  - IL-10 levels increased; CCL17 and IL-16 decreased
  - HDM IgE decreased while IgG4 increased

Sublingual immunotherapy (SLIT)

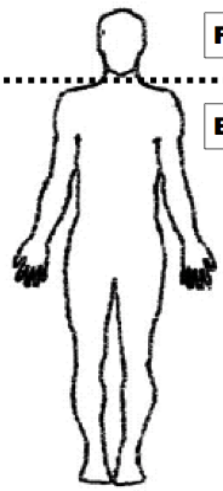
- Pajno et al, JACI 2007 (Italy)
  - Randomized, double-blind, placebo-controlled study of 48 children (5-16 years) with HDM sensitization and AD (SCORAD >7), stratified by disease severity
  - SLIT or placebo for 18 months + standard therapy
  - Significant difference in SCORAD and use of rescue meds found only in patients with mild-moderate AD
  - Severe patients had only marginal benefit
  - SLIT discontinued in 2 patients because of exacerbation of dermatitis

QUESTION: Compliance

- Logistics of lubricating school-aged child interfering with therapy?
- How to sort out all of these medications/ treatments?

ECZEMA ACTION PLAN

** A moisturizer is extremely important. We recommend Aveeno, Nouriva Repair, or Hydrolated Petrolatum twice per day for any patient with eczema.*



		CLEAR	MILD-MOD	SEVERE
FACE	AM	Moisturizer*	Moisturizer* Protopic ointment Hydrocortisone 2.5% oint.	Moisturizer* Hydrocortisone 2.5% oint. Bactroban oint.
FACE	PM	Moisturizer*	Moisturizer* Protopic ointment Hydrocortisone 2.5% oint.	Moisturizer* Hydrocortisone 2.5% oint. Bactroban oint.
BODY	AM	Moisturizer* *May use Protopic ointment or Hydrocortisone 2.5% ointment to any small flare-ups for several days as needed or on the weekends.*	Moisturizer* Protopic ointment Hydrocortisone 2.5% oint. Triamcinolone oint. Bactroban oint.	Moisturizer* Triamcinolone oint. Fluocinonide oint. Bactroban oint. *Call your doctor if not improving after 2 weeks*
BODY	PM	Moisturizer* *May use Protopic ointment or Hydrocortisone 2.5% ointment to any small flare-ups for several days as needed or on the weekends.*	Moisturizer* Protopic ointment Hydrocortisone 2.5% oint. Triamcinolone oint. Bactroban oint. Bath with Balnetar oil Unna Boots	Moisturizer* Triamcinolone oint. Fluocinonide oint. Bactroban oint. Bath with Balnetar oil Unna Boots *Call your doctor if not improving after 2 weeks*

Always check with your doctor before starting or changing any medications or if there are any questions or concerns.

Action Plan

AM:

1. Apply triamcinolone ointment to eczema areas
2. Apply moisturizer everywhere

During day:

1. Apply moisturizer everywhere 1-2 times

PM:

1. Dilute bleach bath for 10 minutes
2. Pat dry
3. Apply triamcinolone ointment to eczema areas
4. Apply moisturizer everywhere

Do this for several days (up to 1 week) until better. Once better…

QUESTION: Miscellaneous

- How to use wet wraps, and how safe are they?
- What is the "best" moisturizer?

Miscellaneous

- Wet wraps, bleach baths, unna boot instructions

www.eczemacarecenter.com

- The best moisturizer is one they will use…
- But… my favorites include the ones with ceramides since I think you can get similar effect to greasier products in less-greasy formulations

What to do when everything seems to fail…

Discussion…

THANK YOU!